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Antidepressants
Monoamines
Receptor sensitivity

Biochimie de la dépression et des antidépresseurs

M. STROLIN BENEDETTI

Résumé. Les voies de synthèse et de dégradation des principales monoamines (dopamine, noradrénaline, sérotonine, phényléthylamine) impliquées dans la pathologie des dépressions sont exposées rapidement. Les variations de l'activité des enzymes responsables des taux sérique, urinaire et cérébrospinal des monoamines et de leurs principaux métabolites sont discutées en relation avec les différents états dépressifs. La modification de la sensibilité des récepteurs neuronaux dans la dépression est ensuite abordée.

Les effets biochimiques spécifiques des inhibiteurs de la monoamine oxydase (IMAO) et des inhibiteurs de la recapture des monoamines sont exposés. Les IMAO sont divisés en inhibiteurs mixtes (A + B) et irréversibles, inhibiteurs spécifiques et irréversibles, inhibiteurs spécifiques et réversibles et leur mécanisme d'interaction avec l'enzyme est également présenté. Les inhibiteurs de la recapture des monoamines sont séparés selon leur spécificité d'action vis-à-vis des monoamines. Le mode d'action de certains antidépresseurs considérés comme atypiques est également abordé. Enfin, l'effet d'un traitement chronique par les antidépresseurs sur la sensibilité des récepteurs noradrénergiques, sérotoninergiques et dopaminergiques pré- et post-synaptiques est discuté.

Biochemistry of depression and of antidepressant action.

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Summary. *The pathways for the synthesis and degradation of the principal monoamines (dopamine, noradrenaline, serotonin, and phenylethylamine) concerned in the pathology of depression are briefly presented. Differences in the activities of the enzymes which control the amounts of monoamines or their principal metabolites in serum, urine or cerebrospinal fluid are discussed in relation to the different types of depression, as is also the role of changes in the sensitivity of neuronal receptors. The specific biochemical effects of monoamine oxidase inhibitors (MAOI's) and of the inhibitors of monoamine re-uptake are considered. MAOI's are classified as irreversible mixed inhibitors (A + B), as irreversible specific inhibitors and as reversible specific inhibitors ; their mechanism of interaction with the enzyme is presented. Inhibitors of monoamine re-uptake are classified according to their specificity for different monoamines. The mechanism of action of some antidepressants which have an atypical mechanism of action is outlined. Finally, the effect of chronic treatment with antidepressants on the sensitivities of the noradrenergic, serotoninergic and dopaminergic pre- and post-synaptic receptors is discussed.*

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Table 385-3 Antidepressants

Name	Usual Daily Dose, mg	Side Effects	Comments
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other meds (except sertraline); akathisia rare	Once daily dosing, usually in A.M.; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
TCAs			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in O.D. (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300		
Clomipramine (Anafranil)	150–300		
Mixed norepinephrine/serotonin reuptake inhibitors			
Venlafaxine (Effexor)	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid-tid dosing; lower potential for drug-drug interactions than SSRIs; contraindicated with MAOIs.
Mirtazapine (Remeron)	15–45	Somnolence; weight gain; neutropenia rare	Once daily dosing
Mixed-action drugs			
Bupropion (Wellbutrin)	250–450	Jitteriness; flushing; seizures in at-risk patients; anorexia; tachycardia; psychosis	Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects
Nefazodone (Serzone)	300–600	Sedation; headache; dry mouth; nausea; constipation	Once daily dosing; no effect on REM sleep unlike other antidepressants
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; anorgasmia; weight gain; hypertensive crisis; tyramine cheese reaction; lethal reactions with SSRIs; serious reactions with narcotics	May be more effective in patients with atypical features or treatment-refractory depressions
Tranylcypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		

NOTE: ADD, attention deficit disorder; MAOI, monoamine oxidase inhibitor; REM, rapid eye movement; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

autonomic responsivity, and social learning. Panic disorder shows familial aggregation, although concordance in monozygotic twins is only 30%. Acute panic attacks appear to be associated with increased noradrenergic discharge in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the α_2-adrenergic antagonist yohimbine and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a neural circuit involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Agents that block serotonin reuptake are therapeutic in preventing attacks. It is theorized that panic-disorder patients have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the "panic attack" mechanism. Accordingly, successful therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

TREATMENT Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medications (Tables 385-3, 385-4, and 385-5). T
antidepressant (TCA) agents imi
clomipramine can benefit 75
panic disorder patients. Low dose
25 mg/d) are given initially to a
creased anxiety associated with
monoamine levels in the initi
treatment. Selective serotonin reu
tors (SSRIs) are equally effectiv
have the adverse effects of T
should be started at one-third to
their usual antidepressant dose (
mg fluoxetine, 25 to 50 mg sertr
paroxetine). Monoamine oxidas
(MAOIs) are at least as effecti
and may specifically benefit p
have comorbid features of atypic
(i.e., hypersomnia and weight gai
orthostatic hypotension, and t
maintain a low-tyramine diet (a
cheese and wine) have limited th
ever. Antidepressants typically
weeks to become effective, an
need to be adjusted according t
sponse.

Because of anticipatory anx
need for immediate relief of pani
benzodiazepines are useful early
of treatment and sporadically the
385-6). For example, alprazolam
0.5 mg qid and increasing to 4 mg
doses, is effective, but patients m
tored closely, as some develop de
begin to escalate the dose of thi
Clonazepam, at a final maintena
to 4 mg/d, is also helpful; its lo
permits twice-daily scheduling,
appear less likely to develop de
this agent.

Early psychotherapeutic inte
psychoeducation aimed at sympto
hances the effectiveness of drug t
tients can be taught breathing te
be educated about physiologic ch
cur with panic, and can learn to
selves voluntarily to precipit
Homework assignments and mo
pliance are important componen
ful treatment. Once patients hav
satisfactory response, drug treatment should be maintai
years to prevent relapse.

GENERALIZED ANXIETY DISORDER Cl
festations Patients with generalized anxiety disorder
persistent, excessive, and/or unrealistic worry associat
signs and symptoms, which commonly include muscle
paired concentration, autonomic arousal, feeling "on edg
and insomnia (Table 385-7). Onset is usually before
history of childhood fears and social inhibition may be
incidence of GAD is increased in first-degree relatives o
the diagnosis; family studies also indicate that GAD and
segregate independently. Over 80% of patients with GA
from major depression, dysthymia, or social phobia. C
stance abuse is common in these patients, particularly
sedative/hypnotic abuse. Patients with GAD readily adm
excessively over minor matters, with life-disrupting eff
panic disorder, complaints of symptoms such as shortn
palpitations, and tachycardia are relatively rare.